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EXAMINER	
SWITZER, JULIET CAROLINE	
ART UNIT	PAPER NUMBER
1634	

DATE MAILED: 07/25/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/761,579	SMITH ET AL.	
	Examiner	Art Unit	
	Juliet C. Switzer	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *30 April 2003* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *11-22* is/are pending in the application.

4a) Of the above claim(s) *17-20, 22* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *11-16 and 21* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

1. This action is written in response to applicant's correspondence submitted 4/30/03. Claims 1-2 and 8 have been canceled, and claims 11-22 have been added. Claims 3-7, 9-10, and 11-22 are pending. Claims 3-7 and 9-10 have been withdrawn from consideration as being drawn to a non-elected invention. Claims 11-22 are subject to a restriction requirement as set forth herein. Applicant's amendments and arguments have been thoroughly reviewed, but are not persuasive for the reasons that follow. Any rejections not reiterated in this action have been withdrawn. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action. **This action is FINAL.**

Election/Restrictions

2. Restriction to one of the following inventions is required under 35 U.S.C. 121:

I. Claims 11-16 and 21, drawn to methods for diagnosing polymorphisms and methods of treatment of a patients, classified in class 435, subclass 6 and class 424, subclass 94.1.

VI. Claims 11-22, drawn to a methods for diagnosing polymorphisms and screening method for determining an association between a treatment and a polymorphism, classified in class 435, subclass 6 and class 436, subclass 501.

The numbering of groups used herein is to be consistent with the restriction requirement already set forth in this application.

The inventions are distinct, each from the other because of the following reasons:

Inventions I and VI are drawn to distinct methods which have different goals and modes of operations. The methods of group I include cancelled claim 8 which was elected previously. Claim 8, previously elected and examined was drawn to the treatment of a patient and required the step of diagnosing a polymorphism and treatment with an effective amount of a PDH drug. The claim was clearly directed at treating a patient for the purpose of treating disease, and was properly classified with methods of treatment. The claims of group VI that do not overlap with the claims of group I (i.e. claims 17-20 and 22) are drawn to a distinct method from those of cancelled claim 8. These claims include a common step of diagnosing a polymorphism, but then include steps to treating the human with an agent that is effective in "some" patients and determining a correlation between the effect of the drug and the polymorphism. These methods are screening methods designed to establish a relationship between a polymorphism and a drug. They require separate search an examination from the previously elected treatment methods. The methods share a common step wherein they utilize the method of diagnosing a polymorphism as set forth in claim 11, and so, claim 11 (and dependents) has been included in each group. Beyond this commonality, however, the methods are distinct from one another because they have different goals and would require different additional process steps, reagents, and analyses for their completion.

Since applicant has received an action on the merits for the originally elected invention, this invention has been constructively elected by original election for prosecution on the merits in this office action. Accordingly, claims 17-20 and 22 are withdrawn from consideration as being directed to a non-elected invention. See 37 CFR 1.142(b) and MPEP § 821.03.

Claim Rejections - 35 USC § 112

3. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

4. Claims 11, 12, 13, 14, 15, 16, and 21 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 11 is indefinite because the preamble of the claim recites a method for determining the presence or absence of a single nucleotide polymorphism, but the final process step of the claim requires a step of testing the sample to determine the identity of the nucleotide. The claims do not clarify how the testing step which results in determining the identity of the nucleotide results in determining the presence or absence of a single nucleotide polymorphism. That is, it is unclear how one practicing the invention knows from the testing step whether one has in fact determined the presence or absence of a single nucleotide polymorphism. Claims which depend from claim 11 are indefinite because they do not remedy this problem.

Claim 11 is further indefinite because it is unclear what is meant by a position "corresponding" to position 1388 of SEQ ID NO: 2, that is, is applicant referring to position 1388 of SEQ ID NO: 2 or are other positions within SEQ ID NO: 2 within the scope of this recitation? To have a position "corresponding" to position 1388 of SEQ ID NO: 2, does a nucleic acid simply have to have 1388 nucleotides or is some other structural limitation implied by the use of this language? Claims 12 and 13 are further indefinite because they refer to "the nucleotide at position 1388 of SEQ ID NO: 2" but the claims from which they depend do not

specifically refer to a particular nucleotide at position 1388 but instead refer to a nucleotide at a position corresponding to position 1388 of SEQ ID NO: 2.

Claims 14-16 are also indefinite for reciting nucleotides "corresponding" to particular positions in SEQ ID NO: 1.

5. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

6. Claims 11-16 and 21 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for detecting and sequencing the human pyruvate dehydrogenase complex E1α (PDH E1α) gene and portions thereof, does not reasonably provide enablement for methods which are limited to the detection of a polymorphism at position 1388 of SEQ ID NO: 2. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

This rejection applies to the instant claims insofar as they might be interpreted as methods for the detection of the presence or absence of particular single nucleotide polymorphisms. Insofar as the instant claims read generally on methods for sequencing the human pyruvate dehydrogenase complex E1α (PDH E1α) gene, this rejection does not apply. The teachings of the specification (at, e.g., page19) and of the prior art as exemplified by Koike et al. disclose methods of detecting and sequencing the PDH E1α gene and portions thereof. Such methods are encompassed by the instant claims as written, and a person skilled in the art

could clearly practice methods of detecting and sequencing a known gene without further guidance. However, it is unpredictable as to whether one of skill in the art could use without undue experimentation methods requiring detection of the polymorphism at position 1388 of SEQ ID NO: 2 or methods for treatment which comprise detection of the polymorphism at position 1388 of SEQ ID NO: 2, which methods are also encompassed by the claims. In addition, the claims encompass further steps wherein nucleotides at positions 26 and 161 of SEQ ID NO: 1. Though many of specific examples herein refer to the elected polymorphism, position 1388 of SEQ ID NO: 2, the inclusion of additional nucleotides in the method do not overcome the concerns.

The instant claims are drawn to methods for the diagnosis of a polymorphism in an PDH E1α gene in a human. The methods comprise steps in which the particular nucleotide present is detected at a particular position in SEQ ID NO: 2. Dependent claims specify the nucleotide present at position 1388 of SEQ ID NO: 2, require the determination of nucleotides present at additional positions in SEQ ID NO: 1, and define some methodologies that can be used for the determining process.

The specification teaches that the genetic abnormalities in the PDH complex are the most common cause of primary lactic acidosis in humans, and that the majority of cases have been linked with a defect in PDH E1α subunit (page 2), and that the activity of PDH is reduced in diabetic patients. Further, the specification provides three polymorphisms in the PDH E1α gene. In particular, the specification teaches a polymorphic site at position 1388 of SEQ ID NO: 2, in the 3' untranslated region of the PDH E1α gene. The specification is silent with respect to the effect of this polymorphism on the biological activity of the PDH E1α gene. The specification

does not disclose any relationship between the presence of this polymorphism a change in the activity or expression of the PDH E1α subunit or between the presence of a particular allele of this polymorphism and any particular disease state or physiological condition.

The prior art provides polymorphisms in the coding portion of the PDH E1α gene. For example, Dahl et al. (Human Mutation, 1 :97-102 (1992)), provides a summary of known PDH E1α mutations (Table 1). These mutations are all within the coding sequence of the PDH E1α gene, and they all result in changes to the encoded polypeptide. The prior art is silent with regard to any polymorphisms in the 3' untranslated region of the PDH E1α gene or within intron 7 of the PDH E1α gene. The prior art does not provide specific guidance with regard to the polymorphism identified herein as being at position 1388 of SEQ ID NO: 2, or the polymorphism present within intron 7.

There is also a large body of knowledge in the prior art related to polymorphisms in general, and their association with diseases or disease states. The art is highly unpredictable with regard to the functionality of polymorphic sites in genomic DNA. After a screening assay identifies polymorphisms, it is unpredictable whether any such polymorphisms would be associated with any phenotypic trait, such as a disease state or a physiological state. For example, Hacker et al. were unable to confirm an association between a gene polymorphism and ulcerative colitis in a case where prior studies suggested such a relationship would exist since the relationship had been identified in a different population (Gut, 1997, Vol. 40, pages 623-627). Even in cases where an association between a particular gene and a disease state is known to exist, such as with the LPL gene and heart disease risk or the β-globin gene and sickle cell anemia, researchers have found that when using SNP (single nucleotide polymorphism analysis)

it was difficult to associate SNPs with disease states or to even identify key genes as being associated with disease (Pennisi, Science, 281 (5384):1787-1789). Finally, in some cases where multiple polymorphisms are identified in a gene, some of these are demonstrated to be disease associated and some are not. Blumenfeld et al. (WO 99/52942) disclose a number of polymorphisms in the FLAP gene. While Blumenfeld et al. were able to demonstrate that some of these polymorphisms are associated with patients having asthma but some of these are not (see Figure 3). For example, the marker 10-35/390 was demonstrated to be associated with asthma, with a p value of 0.00229, while the marker 10-33/327 was determined to not have a statistical association with asthma (p=0.294). Thus, even for SNPs within the same gene, it is highly unpredictable as to whether a particular marker will be disease associated.

Furthermore, with regard to the detection of a nucleotide at position 26 of instant SEQ ID NO: 1, it is highly unpredictable how the information obtained in this portion of the assay will be used, as the polymorphism identified at this portion of the PDH E1α gene is a hexanucleotide repeat, and the first letter of the repeat is "G" and position 26 is the first position of the repeat, and so, the nucleotide present at position 26 will always be "G." It is not known from the specification how detecting the "G" at position 26 would be used.

The level of skill in the pertinent art is quite high, i.e. generally a PhD in biochemistry, but the unpredictability in the art is higher. While the instant specification has disclosed a number of different polymorphisms in the PDH E1α gene, it remains highly unpredictable as to the biological significance of these polymorphisms, particularly the elected polymorphism which is outside of the coding region and has no apparent effect on the encoded gene. Thus, the claimed method directed towards the diagnosis of polymorphisms, or treatment of disease

following diagnosis of polymorphisms, for enablement of the full scope, requires the knowledge of unpredictable and potentially non-existent associations between the instantly elected polymorphism and some phenotypic trait. Even if the elected polymorphism is in some way associated with some disease, it is difficult (if not impossible) to know or predict from the teachings of the specification which disease or how the polymorphism is associated. That is, it is unpredictable as to whether the presence of a particular allele the polymorphism would confer a higher or lower likelihood of having the disease. In this case, the possible uses for the claimed methods are undefined, beyond the suggestion that they can be used to detect a disease associated with the PDH E1α gene prior to treatment with a PDH E1α drug.

The amount of direction or guidance presented in the specification with regard to how to use the instant invention is minimal. With regard to claims directed towards simple detecting the presence of the gene polymorphism, applicant speculates that these polymorphisms "may help to identify patients most suited to therapy with particular pharmaceutical agents (specification, page 3)." However, since the effects of any given polymorphism on gene activity are highly unpredictable, it is impossible to predict from the teachings of the instant specification what identifications can be made using the instantly claimed methods. That is, the specification does not provide any guidance as to how the polymorphism at position 1388 of SEQ ID NO: 2 would be associated with any pharmaceutical agent. The specification does not discuss whether this particular polymorphism will increase the likelihood of a positive or negative response to any drug. Furthermore, with regard to any potential utility in pharmacogenetics, the specification does not provide any guidance as to what disease is in fact associated with the presence or absence of the polymorphism at position 1388 of SEQ ID NO: 2, other than the suggestion that

these methods could be carried out for "PDH E1α mediated diseases." The specification further fails to provide any guidance as to the appropriated PDH E1α drug to be administered after the detection of the polymorphism, or the desired effect of administration of the drug (i.e. to up or down regulate the activity of the gene, and how either of these is to be accomplished). The specification provides no guidance or working examples that teach or demonstrate the ability to use the disclosed polymorphic site as a marker for any disease in particular, or for disease in general, or how to use the disclosed polymorphism to select a proper course of treatment of a disease.

The quantity of experimentation required to discover how to use the instant invention is very high. In order to use the claimed invention, one would have to establish a relationship between the polymorphism at nucleotide 1388 of SEQ ID NO: 2 some physiological or disease state or some disease treatment method. Indeed, even to use the method of claim 1 to identify patients suited for particular pharmaceutical agents, one would need to know that the polymorphism at nucleotide 1388 of SEQ ID NO: 2 was in some way associated with response to some pharmaceutical agent. In order to obtain the type of information necessary to practice the claimed invention, one would be required to undertake the screening of hundreds or thousands of patients as well as possible hundreds of diseases or pharmaceutical agents. Even if such experiments were undertaken, it would still be unpredictable as to whether any associations would be detected, in light of the unpredictability of such associations, as already discussed. Thus, while one could perform further research to determine whether applicant's method would be useful in disease detection and/or treatment, it is unknown as to what the outcome of such research might be and as to whether any quantity of experimentation would result in the

identification of an association between the C/T polymorphism at position 1388 and any disease or condition. Further, absent a teaching the C/T polymorphism at position 1388 is not associated with such conditions, it is further unpredictable as to whether detection of the C/T polymorphism at position 1388 would be useful in predicting, e.g., the absence or decreased likelihood of such conditions.

Thus, in light of the nature of the invention, the state of the art, the high level of unpredictability in the art, the lack of direction or working examples in the specification, and the high quantity of experimentation that would be required to practice the claimed invention, it is concluded that undue experimentation would be required to use the instantly claimed invention. Thus, although the specification certainly enables one to detect the presence of the polymorphism (i.e. the "make" portion of 112 1st paragraph), it would require undue experimentation in order to determine how to use the claimed methods. Considering all of the factors discussed herein, it is concluded that it would require undue experimentation to determine the particular disease state that can be diagnosed and treated and thus to practice the claimed invention commensurate in scope with the present claims.

Claim Rejections - 35 USC § 103

7. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

8. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various

claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

9. Claims 11, 14, 15 and 16 are rejected under 35 U.S.C. 103(a) as being unpatentable over Koike *et al.* (Gene 93 (1990) 307-311).

Koike et al. teach a method for the diagnosis of a polymorphism in an PDH E1α gene in a human which comprises providing a nucleic acid sample wherein the sample comprises a nucleotide at a position corresponding to position 1388 of SEQ ID NO: 2, and testing the sample to determine the identity of the nucleotide. Koike *et al.* further test the sample to determine the identity of nucleotides at positions corresponding to positions 26 and 161 of instant SEQ ID NO: 1 (p. 310 and FIG. 1). Specifically, Koike et al. teach a method for sequencing the PDH E1α gene (p. 310), including the 3' untranslated region and intron 7. At least nucleotides 15974-16246 of the 3' untranslated region of the sequence taught by Koike et al. are identical to nucleotides 1200-1472 of instant SEQ ID NO: 2, thus encompassing the position 1388 of SEQ ID NO: 2. Further, intron 7 taught by Koike *et al.* comprises nucleotides at positions corresponding to nucleotides 26 and 161 of instant SEQ ID NO: 1, for example, intron 7 taught by Koike *et al.* contains a portion (5'-gccggggcaacg-3') which is identical to nucleotides 21-30 of instant SEQ ID NO: 1, thus containing a position corresponding to position 26 of SEQ ID NO: 1. Likewise, intron 7 contains a portion of SEQ ID NO: 1 that is identical to nucleotides 158-170, in other words a position "corresponding" to position 161 of SEQ ID NO: 1. The

teachings of Koike *et al.* expressly include testing the sample (via a sequencing reaction) to determine the identity of all of the nucleotides in the PDH E1α gene, including those specifically recited in the rejected claims.

Koike *et al.* do not teach a method wherein the nucleic acid sample is from a human identified as having or at risk for having a PDH-mediated disease. Koike *et al.* teach that a genetic PDH deficiency has been reported in infants, and that the knowledge of the sequence of the PDH E1α gene will be useful to provide information about the nature of genetic mutations leading to molecular diseases. Therefore, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have sequenced additional samples containing PDH E1α genes from individual having PDH-mediated diseases or at risk of such diseases in order to have added to the body of knowledge concerning the PDH E1α gene. One would have been motivated to undertake such additional sequencing experiments wherein the identity of every nucleotide within the PDH E1α gene is determined in order to have further studied the PDH E1α, possible genetic mutations, and, in order to carry out "studies on the structure of the PDHα cDNA and the PDBβ cDNAs and genes and their expression (p. 310)."

Response to Remarks

Applicant's remarks have been considered but are not fully persuasive.

Previous 112 2nd paragraph rejections are moot because the claims have been cancelled. New 112 2nd paragraph rejections are set forth in view of the newly added claims.

The rejection under 112 1st paragraph is applied herein to the newly added claims, with some minor modifications to address the new claims. Applicants point out that the 3'UTR of a gene affects a variety of operations, and that a polymorphism within the 3'UTR may disrupt a

cis-acting element, create an aberrant cis-acting element, or alter "other" RNA functions by interrupting a crucial RNA structure, such as a hairpin. Further, applicants point out that mutations in the 3'UTRs of various genes have been implicated in a variety of diseases. There is no doubt the myriad of effects that a polymorphism could have on gene expression and function. This is not in dispute. However, all of the possible effects that the polymorphism could have simply underscores the point of the rejection, which is that there is little guidance in the specification or the prior art as to what effects, if any, the polymorphisms being detected by the claimed methods have on the function of the gene they are found in. It is highly unpredictable given all of these possible effects which, if any, would be detected by using the methods of the instantly claimed invention. Applicant has postulated a number of possible effects, but has provided no evidence that any of them would ever be observed in relationship to the polymorphisms disclosed in the instant application. The rejection is therefore applied to the newly added claims.

The rejections under 102(b) have been withdrawn in light of the newly filed claims. A 103 rejection is set forth. Applicant argues that Koika *et al.* do not disclose obtaining a sample form a human having or at risk for having a PDH-mediated disease. This limitation is addressed in the newly set forth rejection.

Conclusion

10. No claims are allowed.

11. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

12. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Juliet C. Switzer whose telephone number is 703 306 5824. The examiner can normally be reached on Monday through Friday, from 9:00 AM until 4:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, W. Gary Jones can be reached on 703 308 1152. The fax phone numbers for the organization where this application or proceeding is assigned are 703 305 3592 and (703) 305-3014.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703 308 0196.

GARY BENZION, PH.D
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600

Juliet Switzer
Patent Examiner
Art Unit 1634

July 14, 2003